Hormones and Prostate Cancer: Current Perspectives and Future Directions

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Prostate cancer is the most commonly diagnosed non-skin cancer in men in most western countries. Despite the high morbidity and mortality from prostate cancer, its etiology remains obscure. Although compelling laboratory data suggest a role for androgens in prostate carcinogenesis, most epidemiologic data on humans are inconclusive. To provide insights and directions for future epidemiologic research on hormones and prostate cancer, this review focuses on current perspectives of serum-based studies and polymorphisms in relevant hormone-related genes. We highlight the importance of methodologic studies and investigations of hormone levels in the prostatic tissue to help clarify the often-contradictory data on serologic studies. We recommend careful analysis and cautious interpretation of studies of genetic markers, including repeats and single nucleotide polymorphisms (SNPs), as false positive and negative results may arise in many current and future studies with limited statistical power and non-representative samples from the population. The review also highlights the reasons to perform functional analyses of SNPs, a critical and often underappreciated component of molecular epidemiologic investigations.

The time is ripe for large-scale multidisciplinary investigations that incorporate molecular genetics, biochemistry, histopathology, and endocrinology into traditional epidemiologic studies. Such collaboration will lead to a deeper understanding of the etiologic pathways of prostate cancer, ultimately yielding better preventive, diagnostic, and therapeutic strategies. *Prostate 52: 213–235, 2002.* Published 2002 Wiley-Liss, Inc.†

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INTRODUCTION

There is a striking difference in prostate cancer risk between different racial and ethnic groups, with African American men having reported incidence rates that are 40- to 60-fold higher than those reported for Asian men [1,2]. Although the reasons for this large disparity in risk are mostly unclear, population differences in androgen levels have been implicated as a possible explanation.

Abundant biological data suggest that androgens play an important role in the development of prostate cancer. For example, the growth and maintenance of the prostate are dependent on androgens, prostate cancer regresses after androgen ablation or anti-androgen therapy, and administration of testosterone induces prostate tumors in laboratory animals [3–5]. However, epidemiologic studies addressing the role of androgens in prostate cancer have produced conflicting data [6,7], due, in part to methodologic limitations, including intra-subject and intra-laboratory variations. With

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the development of molecular endocrinology, epidemiologic studies have recently begun investigating the effects of genetic polymorphisms in hormone-related genes on prostate cancer risk.

This review summarizes current perspectives on androgen metabolic pathways, epidemiologic data on androgenic and non-androgenic hormones and prostate cancer, and polymorphisms of genes involved in androgen metabolism and regulation. Using the current state of knowledge, we attempt to provide insights and directions for future research on hormones and prostate cancer.

CURRENT PERSPECTIVES

Biosynthesis and Metabolism of Androgens in Circulation

Androgens are steroid hormones that induce the differentiation and maturation of the male reproductive organs and the development of male secondary sex characteristics. In men, androgens are formed primarily in the testes and the adrenal gland, and to a lesser extent in peripheral tissues, such as the prostate and skin. Formation of androgens in the endocrine glands occurs by two well-characterized biosynthesic pathways, D4 and D5, each of which begins with the precursor (Figure 1). Testosterone, the principal androgen in circulation, and DHT, the primary nuclear androgen and the most potent androgen, are the two most important androgens in adult males. In blood, roughly 44% of testosterone is bound with high affinity to sex hormone-binding globulin (SHBG), 54% is bound with low affinity to albumin, and only 1–2% of testosterone exists in a free (unbound) state. About 25% of the DHT in the circulation is secreted by the testes, while most (65–75%) arises from conversion of testosterone in peripheral tissue in a reaction catalyzed by the enzyme 5α-reductase or from circulating inactive androgens, such as androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEAS). In humans, two 5α-reductase isoenzymes have been identified. The type 1 enzyme (encoded by the *SRD5A1* gene) is expressed mostly in skin and hair, whereas the type 2 enzyme (encoded by the *SRD5A2* gene) is localized primarily in androgen target tissue, including genital skin and the prostate [8].

Androgen Metabolism Within the Prostate Gland

In men, the prostate is a major site of non-testicular production of DHT, which is derived primarily from testosterone. Free testosterone in circulation enters the prostate cells by passive diffusion, whereas albumin-bound testosterone, because of its low affinity for albumin, can disassociate from albumin, allowing it to enter prostatic cells. The recent identification and characterization of a SHBG receptor in the plasma membranes of prostate cells has led to the suggestion that SHBG-bound testosterone may also enter prostate cells [9,10].

Figure 2 shows the metabolic pathways of androgens within the prostate gland. Within the prostate, testosterone is converted irreversibly to DHT by 5α-reductase type 2. DHT can also be formed from androstenedione by a two-step reduction reaction, in which 5α-reductase converts androstenedione to 5α-androstane-3,17-dione (androstanedione), which is then converted to DHT via 17β-hydroxysteroid dehydrogenase (encoded by the *HSD17B* gene) in a reversible reaction. DHT can further undergo a reversible reduction reaction to form either 5α-androstane-3α, 17β-diol (3α-diol) via the enzyme, 3α-hydroxysteroid dehydrogenase (encoded by the *HSD3A* gene), or 5α-androstane-3β,17β-diol (3β-diol) via the enzyme 3β-hydroxysteroid dehydrogenase (encoded by the *HSD3B* gene). Through the action of glucuronyl transferase, 3α-diol and 3β-diol can be irreversibly conjugated to yield 3α-androstanediol glucuronide (3α-diol G), a terminal metabolite of DHT, and 3β-diol G, respectively. Inactivation of DHT in the prostate by reduction to either 3α- or 3β-diol is an important determinant of intracellular DHT concentration and a potential modulator of androgenic activity in the prostate gland.

The concentration of DHT in serum is only one-tenth that of testosterone, whereas the concentration of DHT in prostatic tissue is several times higher than that of testosterone, suggesting that DHT levels in tissue are important in prostate development and tumorigenesis. However, it is difficult to measure tissue levels of testosterone and DHT in epidemiologic studies, and thus, the concentration of 3α-diol G in serum is commonly used as an indirect measure of 5α-reductase enzymatic activity or, more generally, of intraprostatic androgenicity. The concentration of 3α-diol G in serum correlates well with 5α-reductase activity in genital skin [11,12]. However, serum levels of 3α-diol G are generally thought to reflect enzyme activities of both types 1 and 2 of steroid 5α-reductase. Recent data from studies with finasteride, an 5α-reductase type 2 inhibitor, suggest that serum levels of 3α-diol G may predominantly reflect the type 2 5α-reductase activity, because serum levels of DHT and 3α-diol G decrease concomitantly in men treated with finasteride [13].

Androgenic Action Within the Prostate Gland

The functions of DHT and testosterone in the prostate are mediated by the androgen receptor (AR)

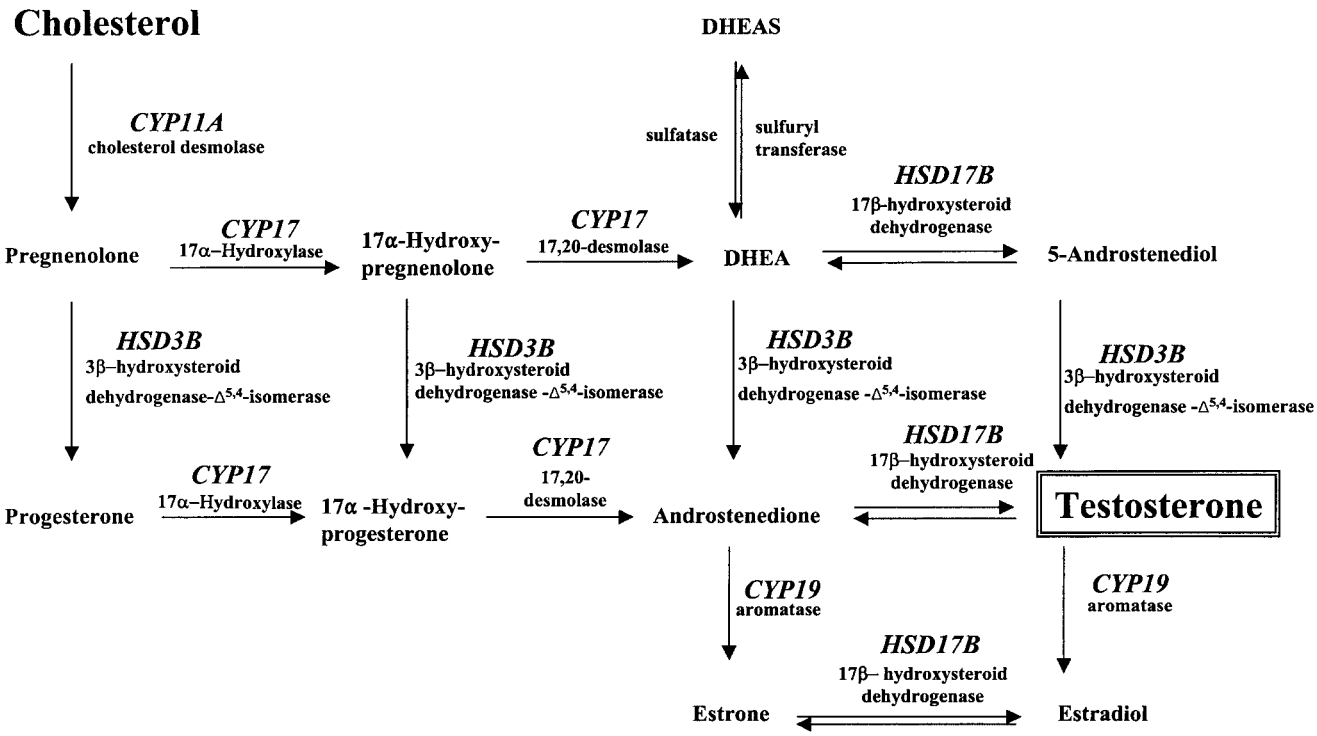

Fig. 1. Biosynthesis and metabolism of androgens. Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.

protein (Figure 3). Within the prostate, DHT binds to the AR to form an intracellular DHT-AR complex, which then binds to the androgen-response elements in the prostate DNA, ultimately inducing DNA synthesis and cellular proliferation. An array of data supports the hypothesis that the AR plays a key role in androgenic action within the prostate gland. Although the tissue concentration of DHT necessary to initiate a

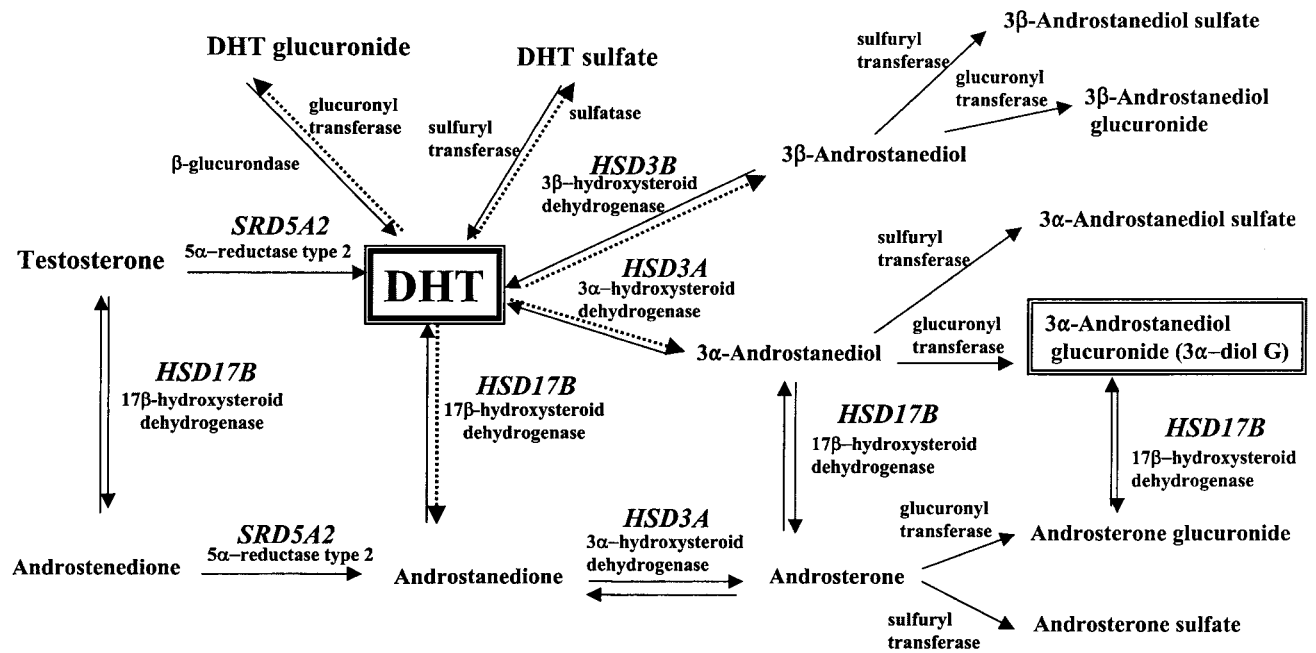

Fig. 2. Metabolism of androgen within the prostate gland. Abbreviations: DHT, dihydrotestosterone; 3α-Androstanediol, 5α-androstane-3α, 17β-diol; 3β-Androstanediol, 5α-androstane-3β, 17β-diol. The dotted line with arrow indicates inactivation of DHT to a less potent androgen.

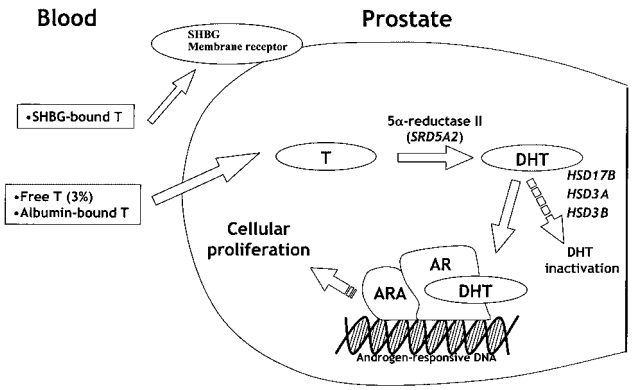

Fig. 3. Androgenic action within the prostate. Androgenic action within the prostate is defined by both the concentration of dihydrotestosterone (DHT) and several other factors, including the level of androgen receptor, androgen receptor coactivators, and growth factors. Abbreviations: T, testosterone; DHT, dihydrotestosterone; AR, androgen receptor; ARA, androgen receptor coactivator.

cascade of androgenic action in the normal prostate is not known, it has been shown that only a minute amount of androgen (mostly from the conversion of adrenal androgen to DHT) is required to trigger androgenic action in prostate cancer patients who have undergone androgen ablation treatment, perhaps because such patients have mutant androgen receptors that are hypersensitive to low levels of serum androgens [14,15]. Experimental data have also shown that in the absence of androgen, non-androgenic hormones (including estradiol, vitamin D, and insulin-like growth factors [IGFs]) in combination with ARs can trigger androgenic action [16,17]. The AR protein is encoded by the AR gene located on the X chromosome. The activity of the AR protein is directly related to the length of the CAG repeat in the AR gene [18] and is further enhanced by the AR coregulatory and associated proteins (AR coactivators). *In vitro* studies have shown that certain AR coactivators, such as ARA54, ARA55, ARA70, ARA160, p160, BRCA1, AIB1, and CBP (cortisol binding protein), can enhance AR transcriptional activity several-fold [19–21].

Thus, androgenic action within the prostate is determined not only by androgen concentration but also by several other factors, such as the levels of the androgen receptor and its coactivators, the presence of growth factors, and perhaps other factors yet to be identified (Figure 3). However, no epidemiologic studies have assessed tissue hormone levels or androgenic action within the prostate directly, due, in part, to the difficulty in collecting prostate tissue from control subjects in case-control studies, or from men at baseline in cohort studies, to measure tissue hormones, steroidogenic enzymes, the AR, or AR coactivators.

Androgens and Prostate Cancer: Epidemiologic Evidence

Studies of androgens in the circulation. Most epidemiologic studies have compared the serum levels of androgens in prostate cancer cases with those in healthy subjects in either case-control or prospective studies. In case-control studies, blood samples from cancer patients are collected after diagnosis (usually before treatment) and assayed for hormone levels. Thus, the presence of disease may have an effect on circulating levels of hormone. Moreover, these types of cross-sectional studies make it difficult to establish a temporal relationship between androgens and prostate cancer. In contrast, prospective studies, such as nested case-control studies, compare serum levels of hormones in pre-diagnostic blood samples from incident cases identified in a prospective follow-up to those of healthy controls selected from the same cohort. Because blood samples of the case subjects are usually collected several years before the diagnosis of cancer, potential effects of disease on the measurement of hormones are presumably minimized.

To date, twelve prospective studies have evaluated the role of serum hormones in prostate cancer (Table I). In most of these studies, the serum concentrations of testosterone and DHT were measured to assess the role of androgens in prostate cancer [22–33]. Although only one study reported a statistically significant association between serum levels of testosterone and prostate cancer [28], several studies found a suggestive, but statistically non-significant, association between prostate cancer and the serum levels of testosterone and DHT [22,24]. In those latter studies, the serum levels of testosterone and DHT were expressed as the ratio of testosterone concentration to DHT concentration, which is used as an indirect measure of steroid 5α-reductase type 2 activity and suggests a role for the 5α-reductase type 2 enzyme [22,24]. More recent studies have found no association between prostate cancer risk and the serum level of 3α-diol G, which is considered a surrogate marker for steroid 5α-reductase activity in the prostate gland [27–33]. In most epidemiologic studies, the failure to show an association between androgen levels and prostate cancer risk may be due, in part, to methodologic limitations that include difficulty in making reliable measurements of circulating hormone levels in an epidemiologic setting. Moreover, the statistical power of some studies is often limited by small sample size, by the observation of relatively small differences (usually 10–15%) between cases and controls, or by fairly large intra- and inter-assay laboratory variations in serum hormone assays [34].

TABLE I. Prospective Studies of Serum Levels of Androgens and Prostate Cancer Risk*

Authors (reference no.)	Study design	Population	No. cases/no. controls	Androgen measured	Results (OR and 95% CI)
Nomura et al., 1988 (22)	Nested case-control	Japanese Americans	98/98	T	0.99[a,b,c]
				DHT	0.66[a,b,c]
Barrett-Connor et al., 1990 (23)	Prospective cohort	U.S. whites	57/951	T	1.00 (0.70 to 1.43)[d]
				Androstenedione	1.26 (1.04 to 1.54)[d]
Hsing and Comstock, 1993 (24)	Nested case-control	U.S. whites	98/98	T	1.5[b,c,d,e]
				DHT	1.0,1.7[b,c,e]
Comstock et al., 1993 (25)	Nested case-control	U.S. whites	81/81	DHEAS	0.94[b]
Carter et al., 1995 (26)	Nested case-control	U.S. whites	16/16	T	[f]
Nomura et al., 1996 (27)	Nested case-control	Japanese Americans	141/141	T	1.03 (0.51 to 2.07)[b,e]
				Non–SHBG-bound T	1.09 (0.48 to 2.51)[b,e]
				DHT	0.82 (0.41 to 1.65)[b,e]
				3d-diol G	1.37 (0.73 to 2.55)[b,e]
				Androstenedione	1.24 (0.62 to 2.47)[b,e]
Gann et al., 1996 (28)	Nested case-control	U.S. whites	222/390	T	2.60 (1.34 to 5.02)[b,e,g]
				DHT	0.71 (0.34 to 1.48)[b,e,g]
				3d-diol G	1.60 (0.93 to 2.76)[b,e,g]
Guess et al., 1997 (29)	Nested case-control	U.S. whites	106/106	T	1.00 (0.75 to 1.34)[h]
				Non–SHBG-bound T	1.14 (0.86 to 1.50)[h]
				3d-diol G	1.16 (0.86 to 1.56)[h]
Vatten et al., 1997 (30)	Nested case-control	Norwegians	59/180	T	0.83 (0.36 to 1.93)[b,e]
				DHT	0.83 (0.36 to 1.94)[b,e]
				3d-diol G	1.10 (0.41 to 2.90)[b,e]
Dorgan et al., 1998 (31)	Nested case-control	Finns	116/231	T	0.80 (0.40 to 1.50)[b,e]
				Non–SHBG-bound T	1.1 (0.6 to 2.1)[b,e]
				DHT	0.7 (0.4 to 1.3)[b,e]
				3d-diol G	1.2 (0.6 to 2.3)[b,e]
				Androstenedione	1.0 (0.5 to 1.9)[b,e]
				DHEAS	1.2 (0.6 to 2.3)[b,e]
Heikkila et al., 1999 (32)	Nested case-control	Finns	166/300	T	1.23 (0.55 to 0.76)[i]
				Androstenedione	0.92 (0.49 to 1.72)[i]
Mohr et al., 2001 (33)	Prospective	U.S. whites	70/1506	T	No association
				DHT	No association
				3d-diol G	0.64 (0.26 to 1.60)[b,e]
				DHEAS	1.47 (0.55 to 3.94)[b,e]

*CI, confidence interval; T, testosterone; OR, odds ratio; DHT, dihydrotestosterone; RR, relative risk; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin; 3d-diol G, 5α-androstane-3α, 17β-diol glucuronide.
[a]OR comparing highest to lowest tertiles.
[b]Adjusted for age.
[c]Result not statistically significant.
[d]RR per 1 standard deviation increase.
[e]OR comparing highest to lowest quartile.
[f]Means of cases and controls not statistically significantly different at each of three different time periods before diagnosis.
[g]Simultaneously adjusted for T, DHT, 3d-diol G, SHBG, and estradiol.
[h]OR per 1 quartile increase.
[i]OR comparing highest to lowest quintile.

TABLE II. Prospective Studies of Serum Levels of Nonandrogenic Compounds and Prostate Cancer Risk*

Hormone	Authors (reference no.)	Study design	Population	No. cases/no. controls	Results (OR and 95% CI)	
Estrone	Nomura et al., 1988 (22)	Nested case-control	Japanese Americans	98/98	0.89[a,b]	
	Barrett-Connor et al., 1990 (23)	Prospective cohort	U.S. whites	57/951	1.09 (0.86 to 1.39)[c]	
	Hsing and Comstock, 1993 (24)	Nested case-control	U.S. whites	98/98	0.8[b,d]	
	Dorgan et al., 1998 (31)	Nested case-control	Finns	116/231	0.8 (0.4 to 1.5)[d]	
	Mohr et al., 2001 (33)	Prospective	U.S. whites	70/1506	No association	
Estradiol	Nomura et al., 1988 (22)	Nested case-control	Japanese Americans	98/98	0.57[a,b]	
	Barrett-Connor et al., 1990 (23)	Prospective cohort	U.S. whites	57/951	1.10 (0.86 to 1.41)[c]	
	Hsing and Comstock, 1993 (24)	Nested case-control	U.S. whites	98/98	1.0[b,d]	
	Gann et al., 1996 (28)	Nested case-control	U.S. whites	222/390	0.56 (0.32 to 0.98)[d,e]	
	Dorgan et al., 1998 (31)	Nested case-control	Finns	116/231	1.1 (0.6 to 2.1)[d]	
	Mohr et al., 2001 (33)	Prospective	U.S. whites	70/1506	No association	
SHBG	Nomura et al., 1988 (22)	Nested case-control	Japanese Americans	98/98	0.85[a,b]	
	Barrett-Connor et al., 1990 (23)	Prospective cohort	U.S. whites	57/951	1.04 (0.80 to 1.34)[c]	
	Carter et al., 1995 (26)	Nested case-control	U.S. whites	16/16	[f]	
	Gann et al., 1996 (28)	Nested case-control	U.S. whites	222/390	0.46 (0.24 to 0.89)[d,e]	
	Dorgan et al., 1998 (31)	Nested case-control	Finns	116/231	0.8 (0.5 to 1.5)[d]	
	Mohr et al., 2001 (33)	Prospective	U.S. whites	70/1506	1.12 (0.44 to 2.87)[d]	
FSH	Hsing and Comstock, 1993 (24)	Nested case-control	U.S. whites	98/98	1.6[b,d]	
	Mohr et al., 2001 (33)	Prospective	U.S. whites	70/1506	No association	
LH	Hsing and Comstock, 1993 (24)	Nested case-control	U.S. whites	98/98	1.8[b,d]	
	Carter et al., 1995 (26)	Nested case-control	U.S. whites	16/16	[f]	
	Mohr et al., 2001 (33)	Prospective	U.S. whites	70/1506	No association	
Prolactin	Hsing and Comstock, 1993 (24)	Nested case-control	U.S. whites	98/98	1.1[b,d]	
	Gann et al., 1996 (28)	Nested case-control	U.S. whites	222/390	1.00 (0.63 to 1.57)[d]	
	Mohr et al., 2001 (33)	Prospective	U.S. whites	70/1506	No association	
Insulin	Stattin et al., 2001 (60)	Nested case-control	Swedes	149/248	6.1 vs. 6.0 mIU/mL[b,g]	
	Hsing et al., 2001 (59)	Case-control	Chinese	128/328	2.81 (1.52 to 5.17)[a,h]	
Leptin	Lagiou et al., 1998 (58)	Case-control	Greeks	43/48	0.70 (0.32 to 1.55)[c,i]	
	Hsing et al., 2001 (59)	Case-control	Chinese	128/328	1.10 (0.59 to 2.07)[a,h]	
	Stattin et al., 2001 (60)	Nested case-control	Swedes	149/298	1.6 (0.8 to 3.2)[j]	
					25(OH)D	$1,25(OH)_2D$
Vitamin D	Corder et al., 1993 (75)	Nested case-control	U.S. whites	181/181	[b,k]	0.15 (0.03 to 0.85)[d,l]
	Braun et al., 1995 (76)	Nested case-control	U.S. whites	61/122	2.4 (0.8 to 8.2)[j]	1.5 (0.5 to 4.5)[d]
	Gann et al., 1996 (77)	Nested case-control	U.S. whites	232/414	0.92 (0.56 to 1.50)[d]	0.88 (0.53 to 1.45)[d]
	Nomura et al., 1998 (78)	Nested case-control	Japanese Americans	136/136	0.8 (0.4 to 1.8)[d]	1.0 (0.5 to 2.1)[d]
	Ahonen et al., 2000 (79)	Nested case-control	Finns	149/596	1.7 (1.2 to 2.5)[m]	ND

*CI, confidence interval; OR, odds ratio; RR, relative risk; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; ND, not determined. (For footnotes, see facing page.)

In addition to these methodologic limitations, it is unclear whether circulating levels of androgens reflect androgenic action within the prostate gland, because DHT in the prostate gland mainly comes from the conversion of testosterone. If serum levels of androgens do not reflect the levels of DHT in tissue, it is difficult to interpret results from serologic studies. Also unclear is whether cumulative exposure to androgens over a lifetime or exposure at certain points in life is more relevant in prostate carcinogenesis. It has been suggested that hormonal changes during the prenatal and peri-pubertal periods may be of etiologic importance, because prostate development, including the substantial differentiation of epithelial cells, occurs at these critical time periods [35]. If early exposure to androgens is most critical for the development of prostate cancer, then most epidemiologic studies that measure circulating levels of hormones in elderly study subjects, who are typically in their sixth decade of life, would miss the etiologically relevant period of exposure.

Studies of androgens in prostatic tissue. A better understanding of the hormonal milieu within the prostate gland and its relationship to circulating hormones is critical to interpret results from serum-based studies. However, no epidemiologic studies have investigated levels of hormones in prostate tissue. The lack of such studies is due mainly to various methodologic problems associated with the collection of prostate tissue for hormone measurements. These problems are further compounded by the lack of a normal comparison group for analytic studies. Under most circumstances, ethical considerations preclude the collection of ''normal'' tissue from healthy subjects. In addition, because of the high prevalence of latent prostate tumors (clinically indolent tumors, stage A_1) in elderly men, the probability of finding histologic evidence of stage A_1 focal tumors among age-matched controls is very high.

Even if the obstacle to collecting optimal tissue could be overcome, the reliable measurement of hormones in tissue is another hurdle that must be addressed. For example, each piece of prostate tissue is likely to differ in texture, the amount of fibromuscular component, the proportion of epithelial cells, and the vascular patterns. Any of these characteristics can affect androgen concentration, sample processing, and the recovery of steroids during the extraction process, which in turn can influence the reproducibility of hormone assays.

Current data on hormone levels in prostate tissue obtained from clinical studies add little to our understanding of the role of hormones in prostate cancer development because most of these studies analyzed very small numbers of patients, used less sensitive and specific assays to measure hormones in tissue, and failed to address several important methodologic issues, such as subject selection and comparability of tissue specimens between subjects. Most of the studies published before 1990 compared tissue hormone levels in patients with prostate cancer to those with benign prostatic hyperplasia. Studies after 1990 focused mainly on the impact of finasteride, a competitive 5α-reductase inhibitor, on serum and tissue levels of androgens.

Non-Androgenic Hormones and Prostate Cancer

The results of studies that link several non-androgenic hormones, including estrogens, insulin, leptin, vitamin D, and pituitary hormones, to prostate cancer are summarized in Table II. The roles of these non-androgenic hormones in prostate cancer risk are not well defined. However, they appear to be involved in androgen biosynthesis and metabolism, and future studies should investigate the individual and combined effects of androgens and these hormones on prostate cancer risk. The role of IGFs has been covered in several comprehesive reviews published elsewhere [36,37].

Estrogens and estrogen receptors. The prostate obtains estrogen from peripheral sources (such as adipose tissue) and through conversion of testosterone to estradiol within its own stroma. Within the prostate, the enzyme estrone sulfatase hydrolyzes estrone sulfate (E_1S) to estrone (E_1), which is readily reduced to estradiol by stromal 17β-hydroxysteroid dehydrogenase (encoded by the *HSD17B* gene) [38,39]. Although estrogen is used as an anti-androgen in the treatment of prostate cancer, the role of estrogen in prostate cancer etiology is unclear. Several lines of evidence suggest that estrogens may enhance prostate carcinogenesis. First, through the actions of SHBG, estrogens may participate with androgen in regulating prostate

[a]OR comparing highest to lowest tertiles.
[b]Result not statistically significant.
[c]Risk estimate for 1 standard deviation increase.
[d]OR comparing highest to lowest quartiles.
[e]Simultaneously adjusted for testosterone, dihydrotestosterone, androstanediol glucuronide, estradiol, and SHBG.
[f]Means not statistically significantly different between cases and controls at each of three different time periods before diagnosis.
[g]Means comparing cases vs. controls.
[h]Adjusted for age, education, and anthropometric factors.
[i]Adjusted for age, education, anthropometric factors, sex hormones, and insulin-like growth factor-I.
[j]OR comparing highest to lowest quintiles.
[k]OR not specified.
[l]Among men with lowest quartile of 25(OH)D.
[m]OR comparing above- to below-median.

growth and function [40]. Second, estrogens may interact with the SHBG receptor in the stroma of the prostate gland to activate IGF synthesis and direct stromal proliferation and, through IGFs, mediate the response of epithelial cells to androgens [41]. Third, experimental studies show that induction of prostate tumors in laboratory rats by administration of testosterone is considerably enhanced by the addition of estradiol, suggesting that estrogens in conjunction with androgens may stimulate the development of prostate cancer [42]. Fourth, prenatal exposure to an extremely low dose of diethylstilbestrol (DES) and other estrogenic compounds significantly affects mouse prostate development *in vivo* and *in vitro* in the presence of androgen [43]. Finally, preliminary reports suggest that offspring of DES-exposed mothers have a higher risk of prostate cancer [44].

Together, these data suggest that estrogens may enhance the risk of prostate cancer. However, Gann et. al. [28] found that higher levels of serum estradiol were associated with a 54% reduced risk of prostate cancer after adjusting for serum levels of testosterone, 3α-diol G, and SHBG. Thus it is possible that at pharmacologic doses, estrogens may have anti-tumor action through their effects on the hypothalamic-pituitary axis, while at physiologic levels, estrogens, alone or in conjunction with androgens, may promote tumor growth.

Estrogen receptors (ERs) mediate the biologic effect of estrogen in the target tissue [45]. It has been suggested that the concentrations of the two distinct ERs, ER-α and ER-β, may affect prostate cancer risk through the influence of the estrogen-ER complex on androgen receptor concentration [46,47]. Although the majority of molecular studies have detected ER-α in stromal cells of the prostate, ER-α is not believed to be highly expressed in prostate carcinoma. ER-β, on the other hand, is highly expressed in prostatic epithelium [45]. Data from a recent study showed that the length of the CA dinucleotide repeat within the ER-β gene influences androgen levels in premenopausal women [48]. Although the effect of ER-β polymorphisms on androgen levels among men has not been studied, preliminary data suggest that ER-β may be involved in the regulation of AR content in the prostate and in epithelial growth, and thus may serve as a physiologic regulator of prostatic epithelial growth and differentiation [49].

Sex hormone-binding globulin. Sex hormone-binding globulin (SHGB) transports androgens and estrogens in the circulation. In the only study to report a definitive positive association between serum levels of testosterone and prostate cancer, Gann et al. [28] found no statistically significant association between prostate cancer risk and testosterone before controlling for serum levels of SHBG. After adjusting for androgen and estradiol, Gann et al. found that serum levels of SHBG were associated with a 54% reduced risk of prostate cancer [28]. Although it is not entirely clear whether adjustment for SHBG is the best way to assess the independent effect of testosterone, the Gann et al. study demonstrates the importance of examining several hormonal factors simultaneously.

Recent data suggest that SHBG may have an effect on carcinogenesis that is independent of its function as a regulator of the free fraction of androgen and estrogen. For example, SHBG mediates steroid hormone signal transduction at the plasma membrane, thereby allowing certain steroid hormones to act without entering the cell by interacting with SHBG membrane receptors [50].

In addition, estradiol can activate the androgen receptor by using SHBG as an intermediate [51]. However, this pathway is complex and not well understood, and the potential independent effects of SHBG have not been investigated fully. Because several factors, such as obesity, estrogens, testosterone, thyroid hormones, insulin, leptin, and IGF-I [52–55], in addition to testosterone, affect circulating levels of SHBG, future studies should measure SBHG along with several other hormones and evaluate its independent effect on prostate cancer risk.

Insulin and leptin. Serum levels of insulin and leptin are associated with obesity and body fat distribution, two putative risk factors for prostate cancer [56,57]. The roles of insulin and leptin in prostate carcinogenesis have been investigated in three case-control studies [58–60]. Two of these studies [58,59] reported no association of serum levels of leptin with prostate cancer risk, while the larger, nested case-control study from Sweden found a positive association [60]. In addition, a recent clinical survey [61] showed that higher plasma levels of leptin were associated with larger (>0.5 cm^3) prostate tumor volumes. One of the two case-control studies investigating the role of insulin in prostate cancer reported a positive association with serum levels of insulin [59]. This association was independent of overall and abdominal obesity as well as serum levels of IGFs, sex hormones, and leptin.

The hypothesis that insulin and leptin may have a role in prostate cancer etiology is biologically plausible and should be evaluated further in prospective studies. In addition to stimulating cell growth through binding to its receptor, insulin may affect prostate tumorigenesis through several potential pathways, including the obesity-sex-hormone pathway, the IGF pathway, the PI3K-Kinase (phosphatidylinositol 3′-kinase-85) signaling pathway, and the apoptotic pathway [62–71]. In the obesity-sex-hormone pathway, insulin increases

the transcription of *CYP17* (the gene encoding the enzyme that is critically involved in the biosynthesis of testosterone) and *CYP19* (the gene encoding aromatase, an enzyme that converts testosterone to estradiol) and decreases the synthesis of SHBG [62–65], thereby increasing the bioavailability of free testosterone for uptake by the prostate gland. Because insulin and IGF have 50% amino acid homology (and their receptors are 60% homologous to each other), insulin can bind to the type I IGF receptor and mediate growth-promoting effects [66–68]. Insulin can also inhibit transcription of IGF binding protein 1, thereby increasing unbound circulating IGF-1 [68]. In recent studies, higher serum/plasma levels of IGF-1 have been linked to an increased risk of prostate cancer [36,37]. Insulin, after binding to its receptor, can activate the insulin receptor substrate, which in turn can activate a cascade of post-receptor events involved in cell survival and proliferation in the PI3-K and apoptotic pathways [69–71]. Although epidemiologic evidence for the association between insulin and prostate cancer is preliminary, the roles of insulin and leptin need to be clarified further because they may provide the missing link between the increased risk of prostate cancer and westernized cultures.

Vitamin D. Vitamin D is a steroid hormone synthesized primarily in skin in response to sunlight exposure. Ecologic studies that demonstrated a correlation between increased sunlight exposure and decreased prostate cancer mortality provided the first link between vitamin D deficiency and prostate cancer [72]. Vitamin D and its analogs have potent antiproliferative, pro-differentiative, and pro-apoptotic effects on prostate cancer cells *in vitro* [73]. In addition, vitamin D inhibits prostate tumor growth *in vivo* [74]. However, despite the strong and consistent laboratory evidence linking vitamin D to prostate cancer, five prospective studies investigating serum levels of vitamin D and prostate cancer risk have produced inconsistent results [75–79] (Table II).

Pituitary hormones. Gonadotropins, such as luteinizing hormone (LH), follicle-stimulating hormone, and prolactin, are secreted by the pituitary and are involved in testosterone production and its feedback control. Gonadotropin-releasing hormone agonists are used to treat prostate cancer [80]. Gonadotropins are not routinely measured in epidemiologic studies because their levels are influenced by pulsatile secretion and diurnal variation, which complicates the assessment of their roles in prostate cancer. Data from one study has suggested that higher serum levels of both LH and testosterone may be associated with an increased risk of prostate cancer risk [24]. There is very little epidemiologic data on the role of prolactin in prostate cancer [24,28,33,81], despite the observation that prolactin mediates the entry of testosterone into prostatic cells *in vitro* and *in vivo* [82]. The biological relevance of gonadotropins to testosterone suggests that their roles in prostate cancer need to be clarified in future studies.

Genetic Susceptibility

Recent epidemiologic stuies have begun to focus on variants of the genes encoding enzymes involved in steroid biosynthesis and metabolism and receptor proteins involved in the androgen metabolic/regulation pathways. Although promising data from these studies are accumulating at a remarkable pace, they are still too sparse to support a role for a specific gene in prostate cancer risk (Table III). Data in the current literature suggests that the frequencies of some polymorphisms in certain genes differ among different racial and ethnic groups. However, whether these genetic variants can help explain part of the large difference in prostate cancer risk between these populations awaits further clarification.

Genes involved in androgen metabolism and regulation. The genes involved in androgen metabolic pathways are shown in Figures 1 and 2. Ross et al. [83] first proposed a polygenic model to help explain the racial/ethnic difference in prostate cancer risk. That model triggered a series of studies that investigated the involvement of genes encoding cytochrome P450 17α-hydroxylase (*CYP17*), aromatase (*CYP19*), 5α-reductase (*SRD5A2*), 3β-hydroxysteroid dehydrogenase (*HSD3B2*), and androgen receptor protein (*AR*) in prostate cancer. Several more candidate genes are discussed in this review. With newly available technology, this list will continue to expand.

CYP17. The enzyme cytochrome P450c17α-hydrolase, which is encoded by the *CYP17* gene (located on chromosome 10q24.3), catalyzes critical steps in the biosynthesis of testosterone. A single base pair change (T to C) in the 5′-untranslated region of the *CYP17* gene (A2 allele) has been linked to male pattern baldness [84], a putative risk factor for prostate cancer. Interestingly, the A2 allele (C nucleotide) of *CYP17* is also associated with higher levels of serum estrone and an increased risk of breast cancer compared to the A1 allele (T nucleotide) of *CYP17* [85]. However, the relationship between *CYP17* and prostate cancer is inconclusive. Of the nine epidemiologic studies that have examined the role of *CYP17* in prostate cancer [86–94], four found a positive association with the A2 allele [86,88,91,93], while two found elevated risk associated with the A1 allele [87,89]. Two studies with data

TABLE III. Studies of Genetic Polymorphisms in Hormone-Related Genes and Prostate Cancer Risk

Gene	Polymorphism	Authors (reference no.)	Study design	Population	Sample size[a]	Results (OR and 95% CI)
CYP17 (10q24.3)	MspA1	Lunn et al., 1999 (86)	Case-control	U.S. whites	108/167	A1A1: 1.0 A2A2: 1.7 (0.7 to 4.1)
		Wadelius et al., 1999 (87)	Case-control	Swedes	178/160	A2A2: 1.0 A1A1: 1.6 (1.0 to 2.5)
		Gsur et al., 2000 (88)	Case-control	Austrians	63/126	A1A1: 1.0 A2A2: 2.8 (1.0 to 7.8)
		Habuchi et al., 2000 (89)	Case-control	Japanese	252/131	A2A2: 1.0 A1A1: 2.6 (1.4 to 4.8)
		Haiman et al. 2001 (90)	Nested case-control	U.S. whites	590/782	A1A1: 1.0 A1A2: 1.04 (0.99 to 1.59) A2A2: 1.17 (0.85 to 1.61)
		Yamada et al., 2001 (91)	Case-control	Japanese	101/200	A1A1: 1.0 A1A2: 2.06 (1.06 to 4.00) A2A2: 2.39 (1.04 to 5.46)
		Chang et al., 2001 (92)	Case-control	U.S. whites	225/283	A1A1: 1.0 A1A2: 1.04 (0.57 to 1.91) A2A2: 1.14 (0.77 to 1.70)
		Kittles et al., 2001 (93)	Case-control	African Americans	71/111	A1A1: 1.0 A1A2: 2.0 (1.0 to 3.9) A2A2: 2.8 (1.0 to 7.4)
		Latil et al., 2001 (94)	Case-control	French	268/156	A1A1: 1.0 A1A2: 0.95 (0.60 to 1.51) A2A2: 0.94 (0.50 to 1.76)
CYP19 (15q21.1)	167–187 base pairs	Latil et al., 2001 (94)	Case-control	French	226/156	167 bp: 1.0 187 bp: 1.41 (1.01 to 1.98)
	Arg264Cys	Modugno et al., 2001 (96)	Case-control	U.S. whites	88/241	CC: 1.0 CT: 1.72 (0.72 to 4.08)
SRD5A2 (2p23)	A49T	Makridakis et al., 1999 (103)	Nested case-control	U.S. blacks & Latinos	388/461	African Americans AA: 1.0 AT/TT: 3.28 (1.09 to 11.87) Hispanic men AA: 1.0 AT/TT: 2.50 (0.90 to 7.40)
		Jaffe et al., 2000 (104)	Case-series	U.S. men	265	A49T is associated with extra capsular disease
		Margiotti et al., 2000 (105)	Case-control	Italian	108/121	AA: 1.0 AT: 7.7 (0.39 to 150.5)
		Latil et al., 2001 (94)	Case-control	French	268/156	AA: 1.0 AT: 0.8 (0.26 to 2.42)
		Hsing et al., 2001 (106)	Case-control	Chinese	170/256	No subject with a T allele
		Mononen et al., 2001 (107)	Case-control	Finns	449/588	TT vs. A/A: 1.04 (0.62 to 1.76)

(Continues)

TABLE III. (*Continued*)

Gene	Polymorphism	Authors (reference no.)	Study design	Population	Sample size[a]	Results (OR and 95% CI)
		Nam et al., 2001 (108)	Case-control	Canadian whites	318/320	
	V89L	Makridakis et al., 1997 (100)	Prevalence survey	95 African Americans 49 Caucasians 40 Latino 102 Asian		VV: African Americans: 59% Caucasians: 57% Latino: 48% Asians: 29% LL: African Americans: 3% Caucasians: 4% Latino: 15% Asians: 22%
		Lunn et al., 1999 (86)	Case-control	U.S. whites	108/156	VV: 1.0 VL: 1.5 (0.8 to 2.6) LL: 1.0 (0.3 to 2.9)
		Febbo et al., 1999 (102)	Nested case-control	U.S. whites	584/799	VV: 1.0 VL: 0.96 (0.76 to 1.20) LL: 0.84 (0.57 to 1.24)
		Jaffe et al., 2000 (104)	Case-series	U.S. men	265	No association with clinical characteristics
		Margiotti et al., 2000 (105)	Case-control	Italian	108/121	LL: 1.0 VV + VL: 0.35 (0.09 to 1.32)
		Yamada et al., 2001 (91)	Case-control	Japanese	92/203	VV: 1.0 VL: 1.13 (0.61 to 2.08) LL: 1.37 (0.70 to 2.71)
		Latil et al., 2001 (94)	Case-control	French	268/156	VV: 1.0 VL: 1.23 (0.80 to 1.88) LL: 2.30 (0.98 to 5.40)
		Hsing et al., 2001 (106)	Case-control	Chinese	186/303	VV:1.0 VL: 0.98 (0.60 to 1.58) LL: 0.88 (0.53 to 1.47)
		Nam et al., 2001 (108)	Case-control	Canadian whites	318/320	LL: 1.0 VL: 2.31 (0.97 to 5.48) VV: 2.76 (1.17 to 6.5)
	R227Q	Hsing et al., 2001 (106)	Case-control	Chinese	176/268	RR: 1.0 RQ: 2.85 (0.25 to 32.1)
	(TA)n repeats	Kantoff et al., 1997 (101)	Nested case-control	U.S. whites	802/590	$(TA)_0/(TA)_0$: 1.0 $(TA)_9/(TA)_9$, $(TA)_{18}/(TA)_{18}$: 0.47 (0.20 to 1.12)
		Margiotti et al., 2000 (105)	Case-control	Italian	108/121	$(TA)_0/(TA)_0$: 1.0 $(TA)_0/(TA)_8$, $(TA)_9/(TA)_9$: 0.95 (0.51 to 1.72)

(Continues)

TABLE III. (*Continued*)

Gene	Polymorphism	Authors (reference no.)	Study design	Population	Sample size[a]	Results (OR and 95% CI)
		Hsing et al., 2001 (106)	Case-control	Chinese	191/304	$(TA)_0/(TA)_0$: 1.0 $(TA)_0/(TA)_9$: 0.67 (0.39 to 1.12) $(TA)_9/(TA)_9$: 0.74 (0.07 to 8.31)
		Latil et al., 2001 (94)	Case-control	French	268/156	$(TA)_0/(TA)_0$: 1.0 $(TA)_0/(TA)_9$: 0.96 (0.58 to 1.56) $(TA)_9/(TA)_9$: 0.50 (0.11 to 2.26)
HSD32 (1p13.1)	$(TG)_n(TA)_n(CA)_n$	Devgan et al., 1997 (113)	Prevalence survey	256 African Americans 248 Euro-Americans 120 Asians	312	
		Chang et al., 2002 (116)	Case-control and family study	U.S. whites	159 hereditary cases 245 sporadic cases 222 controls	B1: N367T or B2: c7519g were associated with higher risk
AR (Xq11-12)	CAG repeats	Irvine et al., 1995 (118)	Prevalence survey	Normal subjects: 45 African Americans 39 non-Hispanic whites 39 Asians 68 prostate cancer cases (U.S. whites)	191	>22: 1.0 <22: 1.25
		Hardy et al., 1996 (119)	Cross-sectional	U.S. whites	109	A shorter repeat is associated with younger age at diagnosis
		Stanford et al., 1997 (120)	Case-control	U.S. whites	301/277	≥ 22: 1.0 <22: 1.23 (0.88 to 1.73)
		Giovannucci et al., 1997 (121)	Nested case-control	U.S. whites	587/588	≥ 26: 1.0 ≤ 18: 1.52 (0.92 to 2.49)
		Edwards et al., 1999 (122)	Case-control	British whites	178/195	≤ 21: 1.00 >21: 1.00 (0.96 to 1.03)
		Sartor et al., 1999 (124)	Prevalence (no cancer)	65 U.S. blacks & 130 whites		Mean CAG repeat: White: 21; blacks: 19
		Bratt et al., 1999 (125)	Case-control	Swedes	190/186	A shorter repeat was associated with younger age at diagnosis and high-grade, high-stage tumors
		Correa-Cerro et al., 1999 (126)	Case-control	French & German whites	132/105	≥ 22: 1.0 <22: 1.2 (0.7 to 2.0)

TABLE III. (*Continued*)

Gene	Polymorphism	Authors (reference no.)	Study design	Population	Sample size[a]	Results (OR and 95% CI)
		Lange et al., 2000 (127)	Case-control	U.S. whites	270	≤ 21:1.0 > 21: 0.85 (0.53 to 1.35)
		Nam et al., 2000 (128)	Case-series	Canadian men	318	> 18: 1.0 < 18: 8.07 (2.02 to 32.2)
		Xue et al., 2000 (129)	Case-control	U.S. whites	57/156	≥ 20: 1.0 < 20: 1.97 (1.05 to 3.72)
		Hsing et al., 2000 (130)	Case-control	Chinese	189/301	≥ 23: 1.0 < 23: 1.65 (1.14 to 2.39)
		Latil et al., 2001 (94)	Case-control	French	268/156	> 24: 1.0 ≤ 20: 1.1 (0.60 to 2.02)
		Modugno et al., 2001 (96)	Case-control	U.S. whites	449/558	≥ 23: 1.0 < 23: 1.75 (1.05–2.94)
		Beilin et al., 2001 (132)	Case-control	Australia	448/456	every 5 CAG repeats: 0.98 (0.84 to 1.15)
		Panz et al., 2001 (133)	Case-control	South Africa 40 Africans and 40 whites	40/40	Cases had a shorter repeat length than controls (20 vs. 23)
	GGN repeats	Irvine et al., 1995 (118)	Prevalence survey	U.S. men	191	16: 1.0 non-16: 1.18
		Stanford et al., 1997 (120)	Case-control	U.S. whites	301/277	≥ 16: 1.0 < 16: 1.60 (1.07 to 2.41)
		Platz et al., 1998 (123)	Nested case-control	U.S. whites	582/794	< 23: 1.0 > 23: 1.12 (0.71 to 1.78)
		Edwards et al., 1999 (122)	Case-control	British whites	178/195	≤ 16: 1.0 > 16: 1.06 (0.57 to 1.96)
		Hsing et al., 2000 (130)	Case-control	Chinese	189/301	≥ 23: 1.0 < 23: 1.12 (0.71 to 1.78)
AIB1 (20q12)	CAG/CAA repeats	Platz et al., 2000 (139)	Case-control	U.S. whites	581/786	28/29: 1.0 29/29: 1.03 (0.77 to 1.37) 28/28: 1.10 (0.79 to 1.53)
		Hsing et al., 2002 (138)	Case-control	Chinese	189/299	29/29: 1.0 29/30,31,32: 1.58 (0.62 to 4.01) 29/28: 1.30 (0.83 to 2.03) 28/28: 2.12 (1.09 to 4.12)
ER	XbaI, PvuII	Modugno et al., 2001 (96)	Case-control	U.S. whites	88/241	XbaI +/+: 1.0 +/−: 1.39 (0.81 to 2.39) −/−: 1.22 (0.54 to 2.71) PvuII: +/+: 1.0 +/−: 1.01 (0.57 to 1.83) −/−: 1.60 (0.81 to 3.12)

on circulating levels of hormones found no correlation between *CYP17* polymorphisms (either the A1 or A2 alleles) and serum levels of testosterone and 3α-diol G [90,96]. These results suggest that the effect of *CYP17* on prostate cancer, if any, is likely to be small.

CYP19. The *CYP19* gene (located on chromosome 15q21.1) encodes for the key steroidogenic enzyme aromatase that catalyzes the irreversible conversion of androstenedione to estrone and testosterone to estradiol. Aromatase is present in the gonads and in the extragonadal organs and tissue, including the prostate and adipose tissue. In men, conversion of androgen to estrogens occurs mostly in the adipose tissue. Two studies have investigated the role of *CYP19* in prostate cancer [94,95]. One found a positive association with the tetranucleotide repeat (TTTA)n in intron 4 of the *CYP19* gene [94] and the other reported that polymorphism of ARG264Cys (the C to T substitution in exon 7 resulting in a single amino acid substitution from Arg by Cys at codon 264) [95] was associated with a non-significant 72% increase in the risk of prostate cancer.

SRD5A2. Cross-sectional surveys showed that African American and Caucasian men have higher serum levels of 3α-diol G than native Japanese men [97]. In addition, Chinese men have a much lower chest hair density (a surrogate measure of 5α-reductase type 1 activity) than western men [98]. Because serum levels of 3α-diol G and body hair reflect steroid 5α-reductase activity, these observations led to the hypothesis that population differences in 5α-reductase activity and/or the polymorphisms of the *SRD5A2* gene, which encodes 5α-reductase, may be related to the development of prostate cancer and may contribute to part of the racial/ethnic differences in risk [83].

More than 22 mutations, including 10 single amino acid missense substitutions, have been reported for *SRD5A2* [99]. Four of these mutations—A49T (a substitution of threonine for alanine at codon 49), V89L (a substitution of leucine for valine at codon 89), R227Q (a substitution of glutamine for arginine at codon 227), and a $(TA)_n$ dinucleotide repeat—have been investigated for their association with prostate cancer in twelve epidemiologic studies that have produced mixed results (Table III) [86,94,100–108]. Of the seven studies investigating the A49T marker in the *SRD5A2* gene, two [103,105] reported a statistically significant association between the A49T mutation and prostate cancer, one reported that the A49T genotype was associated with more aggressive prostate cancer [104], while others did not find any association [94,106–108]. Nine studies investigated the association between the V89L marker and prostate cancer risk and four examined the role of $(TA)_n$ repeat length in prostate cancer, with most of the studies reporting no association with these polymorphic markers. The R227Q mutation, which is related to male pseudohermaphroditism, has been detected only in Asians. The only study investigating the role of the R227Q mutation found no association with prostate cancer risk [106].

The inconsistent findings for the *SRD5A2* markers in various studies are largely due to the low frequency of certain mutant alleles of some markers in the *SRD5A2* gene. For example, other than the V89L mutation, the frequency of the mutant alleles in various markers (including A49T and R227Q) is less than 5%, limiting the power of detection. Larger studies in various racial/ethnic groups are needed to further elucidate the hypothesis that polymorphism of the *SRD5A2* gene is associated with prostate cancer risk. Although epidemiologic data on the role of *SRD5A2* in prostate cancer are inconclusive, the aggregate of the data suggests that relative to western men, Asian men have a higher prevalence of the LL genotype of the V89L marker and that the LL genotype is associated with lower serum levels of 3α-diol G [96,106,108].

***HSD3B* and *HSD17B*.** Incomplete activation or slower degradation of DHT within the prostate can lead to the accumulation of DHT and, perhaps, increased androgenic action. Thus, enzymes that inactivate DHT may be of etiologic importance for prostate cancer. As shown in Figure 2, at least three enzymes, 17β-hydroxysteroid dehydrogenase type III (encoded by the *HSD17B3* gene), 3α-hydroxysteroid dehydrogenase (encoded by the *HSD3A* gene), and 3β-hydroxysteroid dehydrogenase (encoded by the *HSD3B* gene located on chromosome 1p13.1), are involved in the metabolism of DHT within the prostate [109–114]. Polymorphisms in these genes, such as a dinucleotide repeat polymorphism in the *HSD3B* gene [113], have been reported. Although epidemiologic investigations of these polymorphisms are actively underway, no data on the risk of prostate cancer and these genes have been published.

AR and AR coactivators. The androgen receptor is expressed in all histologic types and stages of prostate cancer [115]. Numerous somatic mutations in the *AR* gene have been reported among prostate cancer patients enrolled in clinical studies. Most of these mutations have been detected in tumor tissue of late-stage prostate carcinoma, with consistent findings showing that somatic mutation of the *AR* gene is involved in the progression and aggressiveness of prostate cancer [115].

Fifteen studies have investigated the role of CAG (coding for polyglutamine) and GGN (coding for

glycine) repeats in prostate cancer and have produced inconsistent results (Table III) [94,95,116–131]. For example, four studies showed that men with a shorter CAG repeat length were at higher risk of prostate cancer [118,119,126–128], whereas others did not confirm these findings [94,120,125,130]. In all of these studies, however, the length of CAG repeats corresponded to racial variation in prostate cancer risk; that is, African Americans, who have a high risk of prostate cancer, had a shorter CAG repeat length, Caucasians had an intermediate repeat length, and Asian men, who have a much lower risk of prostate cancer, had a longer repeat length. Laboratory studies have shown that a shorter CAG repeat length is associated with an increased transactivation of AR [18]; however, the biological role of GGN repeats is less clear. Five studies that measured GGN repeats found that men with a GGN repeat length other than 23 had an increased risk of prostate cancer [116,118,120,121,128].

Two other polymorphisms in the *AR* gene have been investigated for their associations with prostate cancer: the R726L mutation (a substitution of leucine for arginine at codon 726) in exon S of the *AR* gene and the Stu I single nucleotide polymorphisms, designated the S1 and S2 alleles, which correspond to the absence and presence, respectively, of a diagnostic cleavage site for the Stu I restriction endonuclease. The R726L mutant allele is in linkage disequilibrium with the long CAG repeat length in the *AR* gene, in that all subjects with the R726L mutant allele have a 26 CAG repeat length (the median CAG repeat length in Caucasian populations ranges from 20 to 22) [129]. The R726L polymorphism, which alters the specificity of the AR protein, was found at higher frequency than other alleles among prostate cancer patients in two clinical surveys, and a separate study linked the R726L mutation to an almost 6-fold increased prostate cancer risk in Finnish men [129]. To date, the R726L mutation has only been reported in Finnish populations. The S1 Stu I allele was associated with a 3-fold higher prostate cancer risk among African Americans under the age of 65 years. In addition, *AR* polymorphisms (both CAG repeat length and the S1 Stu I allele) have been linked with male pattern baldness [132–135], a clinical condition that has been linked to higher levels of DHT and prostate cancer risk.

AR coactivators enhance transactivation of AR several fold (19) and therefore potentially increase the risk of prostate cancer. One AR coactivator is encoded by the *AIB1* (Amplified in Breast Cancer 1) gene, which has two distinct CAG trinucleotide repeats. Two epidemiologic studies have investigated the role of *AIB1* in prostate cancer: one found a positive association between AIB1 CAG repeat length and prostate cancer [136], and the other reported no association [137]. Future studies should investigate the combined effects of AR and AR coactivators in prostate cancer risk.

Estrogen receptor. One study in Australia investigated the Xba^1 and PvuII markers in the estrogen receptor gene and reported a 5-fold prostate cancer risk among men homozygous for the ER XbaI genotype and a shorter CAG repeat length in the androgen receptor gene [95].

Limitations of Studies of Genetic Polymorphisms

The molecular characterization of genetic markers provides an opportunity to examine disease at the cellular level. Compared to serum-based studies, this approach has two distinct advantages. First, molecular assays usually, but not always, produce more qualitative (categorical) results with higher reproducibility than the continuous data typically produced by serologic assays. Second, unlike serologic markers in cross-sectional case-control studies, genetic susceptibility status (i.e., genotype) is not affected by the presence or process of disease or by other exposures that may change over time.

Despite these advantages, studies of genetic polymorphisms have their own limitations. First, most of the current studies have limited statistical power because fewer than 500 subjects are typically analyzed and the allele frequency of certain markers within the study population is less than 5%. Second, because most current studies also lack the power to evaluate the combined effect of several genes, they cannot produce a comprehensive picture of genetic predisposition and cancer risk. Third, risk estimates can be influenced by confounding, by selection of study subjects (such as inclusion of surviving cases only), by multiple comparisons of the enormous number of allelic variants (including a large number of SNPs and mutations in several markers of the same gene), and by linkage disequilibrium.

Finally, most current molecular epidemiologic studies investigate common polymorphisms in specific genes without considering the functional consequences of those polymorphisms, making the results of such studies difficult to interpret. For example, a particular association between a specific genetic marker and prostate cancer risk may be mechanistically significant or may merely reflect linkage of this marker to another truly causative marker. These kinds of uncertainties may explain at least some of the often-contradictory outcomes of molecular epidemiologic studies reported in the literature. The recent proliferation of studies on genetic polymorphisms will result in a flood of genetic data and many false positive associations. We suggest that care be taken in the interpretation of these data.

FUTURE DIRECTIONS

Prostate cancer is a heterogeneous disease (in terms of biological behavior) and it is likely that a more complete picture of its etiology related to hormones will require an understanding of the complex biological interactions among hormones, hormone-metabolizing genes, receptor proteins, and exogenous factors. Thus, an array of studies is needed to address these issues in the future. These include methodologic studies of tissue hormone levels, cross-sectional studies conducted in several racial/ethnic populations simultaneously with a common protocol, and additional serum-based nested case-control studies with more sensitive and specific assays, such as liquid chromatography-mass spectrometry [138], that are large enough to investigate multiple hormones and hormone metabolism genes simultaneously. Figure 4 summarizes various approaches needed to address these issues.

Studies of Prostate Tissue

To help understand further whether circulating levels of hormones reflect androgenic action within the prostate, well-designed rigorously conducted methodologic studies should be carried out to collect high quality snap-frozen normal prostate tissue for the measurement of tissue hormones, enzymatic activities, and receptor proteins so that an overall index of androgenicity in the prostate can be derived. Because such studies are logistically challenging, meticulous attention should be paid to details related to establishing the infrastructure for subject selection, tissue procurement and collection procedures, preservation of samples, and validation of hormone assays. In addition, quality control procedures should be implemented to evaluate intra-prostatic as well as intra- and inter-assay variations in tissue hormones. Once tissue hormone assays have been validated, it will be essen-

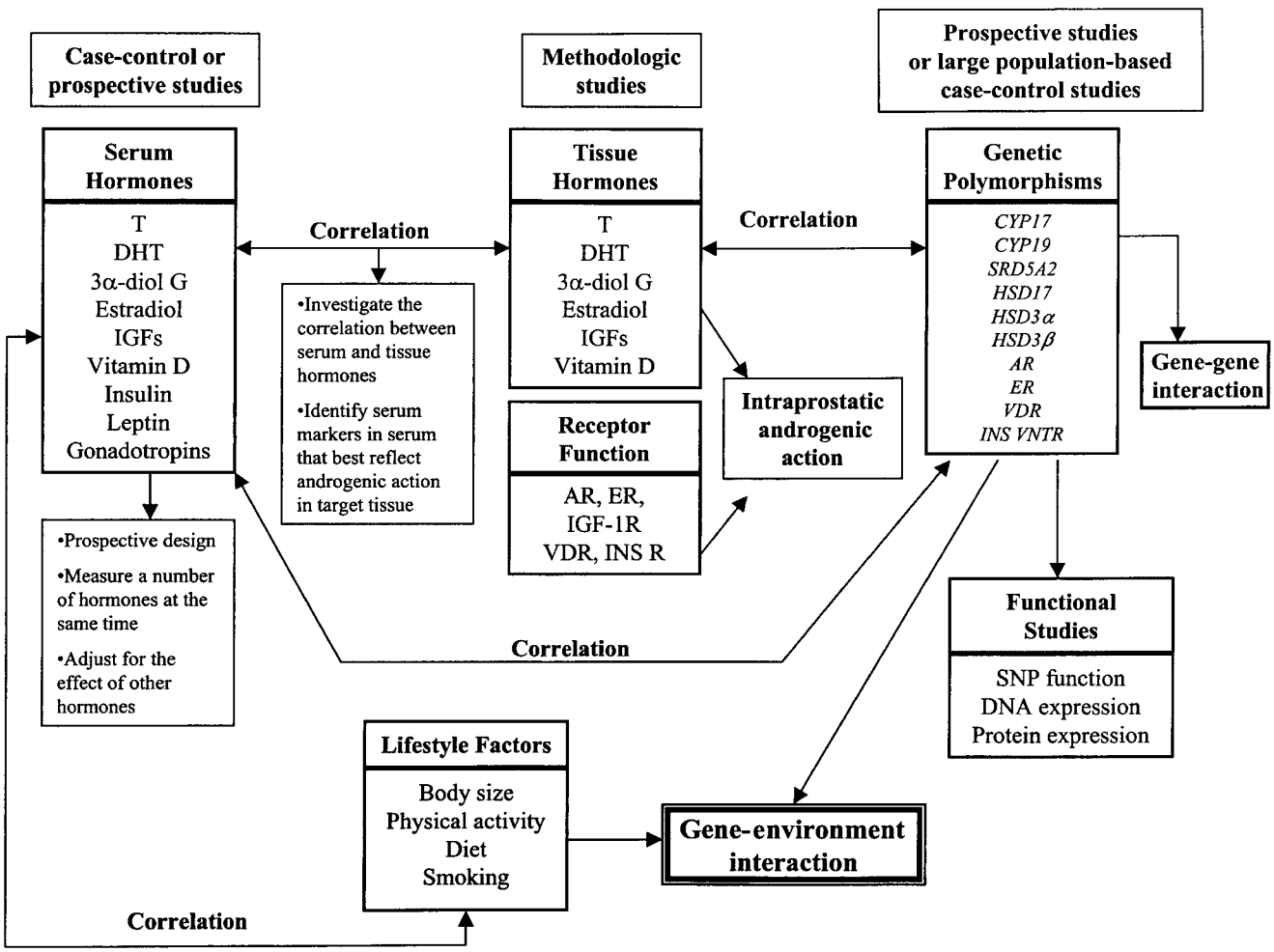

Fig. 4. Suggested future research on hormones and prostate cancer. A summary of an array of methodologic and analytic studies to further clarify the role of hormones in prostate cancer.

tial to assess whether smoking, alcohol use, body size, and lifestyle factors affect tissue levels of hormones. Racial or ethnic differences in tissue levels of hormones should also be evaluated after taking into account lifestyle and other potential confounding factors. An ongoing study is currently evaluating these issues (Hsing AW, Hemstreet G, Levine P, Zolfghari L, Veneroso CC, Stewart K et al., unpublished data).

Correlations between serum and tissue levels of hormones would provide insights into whether intraprostatic metabolism is more relevant to the etiology of prostate cancer than serologic measurements. We therefore recommend that in these types of methodologic studies, fasting blood samples be collected on the same day the tissue is procured so that circulating levels of hormones can be measured and compared to tissue levels. If large enough tissue samples can be collected, metabolism studies should be carried out to determine the ratio of testosterone to DHT in tissue, which is thus far the best possible measure of 5α-reductase activity in the prostate. Ultimately, it would be useful to know whether there are any racial or ethnic differences in the serum-tissue correlation because the identification of such differences would validate the 5α-reductase hypothesis.

It would also be useful to correlate tissue levels of hormones with genetic variants to provide insights into the functional significance of these polymorphic markers. To do so, peripheral lymphocytes or buccal cells should also be collected in the same studies that procure prostate tissue for hormone assays. Such cells could be used for the extraction and analysis of genomic DNA to determine whether tissue hormone levels (phenotypes) correlate with genetic polymorphisms (genotypes) of hormone-metabolism genes.

Studies of Hormone Levels in Serum

Because it is not feasible to compare tissue hormone levels in case and control subjects or to measure tissue hormone levels at baseline in cohort studies, future studies will continue to rely on serum-based assays of hormone levels. Nevertheless, efforts should be made to minimize variation in assays and sampling in future studies. These measures should include the use of more sensitive and specific assays to minimize measurement error and characterize hormonal status more accurately in study subjects; the simultaneous measurement of several hormones in the same study to provide a more complete hormonal profile of each study subject so that the net effect of each hormone can be assessed; the standardization of time of blood collection so that diurnal and seasonal variation in hormone levels among study subjects can be minimized; and the use of a large enough sample size (preferably several hundred case-control pairs from prospective studies) to yield sufficient statistical power. In addition, it is important to have a better understanding of factors that affect circulating levels of hormones so that appropriate statistical analyses can be conducted to control for confounding. For example, methodologic studies examining relationships between epidemiologic factors, such as anthropometry, physical activity, and diet, and the interrelationships among hormones, including androgens, estrogens, IGFs, SHBG, leptin, and insulin, should be carried out to provide critical data to help refine the analytical models in the statistical analyses. Because the validity of the results hinges on the quality of hormone assays, we cannot stress enough the importance of optimizing hormone measurements in future studies. Imperfect as they may be, serum levels of hormones, if measured accurately, presumably reflect the combined effects of genetic polymorphisms as well as other genes and exogenous factors.

A better understanding of how serum hormone levels vary in different racial and ethnic populations may shed light on the etiology of prostate cancer. In addition, studies that compare the levels of circulating hormones between low- and high-risk populations in various decades of life may be useful to identify critical time periods in life that are etiologically relevant to prostate cancer risk. Previous studies have suggested that in utero exposure to testosterone may explain the excess prostate cancer risk in African American men, because levels of testosterone in pregnant black women are higher than those in pregnant white women [139]. Comparisons of hormone levels in cord blood from various racial/ethnic groups may provide additional insights into this hypothesis. These suggested methodologic studies, although cross-sectional in nature, should be guided by sound epidemiologic principles and include probability samples from each population in order to provide solid data to aid in the interpretation of results from future prospective studies.

Studies of Hormone-Related Genes, Gene-Gene and Gene-Environment Interactions

Although linkage studies have identified several susceptibility genes with high penetrance in prostate cancer, including—*HPC1, PCAP, HPCX, CAPB*, and *HPC20* [140–149], these genes have relatively low ($< 10\%$) frequency and are thought to account for only 8–10% of the prostate cancer cases (hereditary cases) in the population. Obviously, differences in these rare genetic loci are not likely to explain the large differences in prostate cancer risk between different racial/ethnic groups. In contrast, allelic variants in low-

penetrance cancer-susceptibility genes (i.e., common polymorphisms) involved in androgen regulation and metabolic pathways such as the ones reviewed earlier, although having much lower impact on cancer risk, may affect a larger fraction of the population. Thus, they may potentially account for a larger proportion of prostate cancer in the general population and explain part of the large racial/ethnic difference in risk. However, it is unlikely that a single polymorphism will have a profound effect on androgen levels or prostate cancer risk because genes tend to act in concert with other genes. The current view is that alterations in multiple genes, rather than in a single gene, may affect intraprostatic androgenicity, thus heightening prostate cancer risk in a subset of individuals. Therefore, with new technology a set of common polymorphisms of several susceptibility genes involved in androgen metabolism or signal transduction pathways (Figure 2), should be assessed simultaneously in a large number of samples so that the combined effects of multiple markers in the same gene or multiple gene (gene-gene interactions) on prostate cancer risk can be evaluated.

Furthermore, since prostate cancer is likely to result from a complex interplay of genetic and environmental factors [148], and since the expression of genetic traits is likely to be influenced by exogenous factors, ultimately large studies (several thousand cases) with high-quality biological samples in well-characterized populations should be conducted to investigate interactions between genes and the environment in order to provide a more complete view of genetic predisposition and to identify susceptible subgroups for early detection.

SUMMARY

In summary, although many pieces of the puzzle in our understanding of prostate cancer are still missing, promising clues are emerging. With newly available technology, exposure assessment and disease classification can be refined further for hypothesis testing. A wealth of new data, including hormone levels in various biological samples, a number of genetic polymorphisms, and somatic alterations, will soon become available and may reveal more specific exposure-disease relationships. The aggregate of these data will enhance our understanding of hormonal carcinogenesis in prostate cancer and help solve the puzzle. Such efforts, however, require an interdisciplinary approach that combines the efforts of investigators across several disciplines, including epidemiology, urology, pathology, biochemistry, endocrinology, genetics, and molecular biology. To break new ground in the etiology of prostate cancer, the next generation of studies should be large-scale well-executed epidemiologic studies of sound design and sufficient sample size that collect and analyze high-quality biologic samples. Such studies will provide unique opportunities to incorporate state-of-the-art techniques to test emerging hypotheses in a timely fashion.

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